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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/021,403	12/12/2001	Robert J. Schwartz	108328.00031	3652

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EXAMINER	
HAMA, JOANNE	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 02/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/021,403	SCHWARTZ ET AL.	
	Examiner	Art Unit	
	Joanne Hama, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 December 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-13,76,79-88,137 and 138* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-13,76,79-88,137 and 138* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response to the First Action on the Merits filed on 12/07/04 is acknowledged.

Claims 2, 3, 77, 78 have been cancelled. Claims 1, 11, 76, 86 have been amended. Claims 137 and 138 are newly added.

Claims 1, 4-13, 76, 79-88, 137, 138 are under consideration.

Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Applicants have amended the specification and the application is now in sequence compliance.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-13, 76, 79-88, 137, 138 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of improving or enhancing growth or rate of growth in an offspring of a pregnant non-human mammal female, comprising, introducing in the female sow intramuscularly during third trimester of gestation of said offspring a vector comprising a muscle specific promoter operably linked to the nucleotide sequence disclosed in SEQ ID NO 1 or SEQ ID NO 8 wherein said nucleotide sequence is operably linked to a HGH 3' untranslated region, wherein

said nucleotide sequence is expressed in the female and wherein the expression of said nucleotide sequence results in improved or enhanced growth or rate of growth of the offspring, does not reasonably provide enablement for other embodiments of the claimed invention for reasons of record set forth in the previous Office Action of 8/5/04.

Response to Arguments

Applicant's arguments filed 12/7/04 have been fully considered but they are not persuasive.

There appears to be some discrepancy as to what is meant by "in utero" in "in utero gene therapy." The Applicant has defined "in utero gene therapy", based on a definition from Zanjani and Anderson as, "gene transfer in the fetus (Applicant's Response, page 17 bottom to page 18 top)." Further, the Applicant states that Examiner's definition of "in utero gene therapy" as "any nucleic acid linked to any promoter and any 3' UTR is introduced into any animal at any time (before, after, or during pregnancy) by any method/route so as to increase growth of the offspring," is broad. In fact, "better nutrition or consumption of food positively correlates with high birth weights and increased growth of offspring, would be a form of "in utero fetal gene therapy...(as) food contains highly variable quantities of genomic material (i.e. any nucleic acid linked to any promoter and any 3'UTR) and is introduced into the mother at any time, before, after, or during pregnancy, by any method of route (Applicant's Response, page 18, first paragraph, lines 7-12)."

In response to what the Applicants assert as to what is meant by "in utero," as defined by Zanjani and Anderson, the Examiner had intended "in utero" to mean "while pregnant." Regardless of what "in utero" should mean, the Examiner in the previous Office Action analyzed the issue of gene therapy at the time of the invention and that **any nucleic acid linked to any promoter and any 3' UTR was introduced into any animal at any time (before, after, or during pregnancy) by any method/route so as to increase growth of the offspring** was not enabled. The focus of this argument is that according to the art at the time of filing, there was no way to predict that introducing any nucleic acid linked to any promoter and any 3' UTR to an animal would necessarily have an effect on increasing the growth of the offspring. This is because there are several elements of gene therapy in which a skilled artisan has no control. As pointed out by Zanjani and Anderson (1999, Science, 285: 2084-2088, provided by Applicant as part of Applicant's Response) some common considerations of gene therapy include: are enough genes are transferred into the cell, will expression from the transferred gene be at the correct level and for an adequate duration, will it be regulated appropriately, and will the gene product be eliminated by the immune system or by some other mechanism (Zanjani and Anderson, page 2086, 3rd col., 3rd parag.)? The Applicant's argument or specification do not provide any specific guidance to address the issues raised by Zanjani and Anderson or other art that discuss the state of the art of gene therapy at the time of filing of the invention.

The arguments regarding Khan et al. (2002, Endocrinology) is an excellent example of demonstrating that gene therapy is unpredictable and does not enable a

skilled artisan to use "any nucleic acid linked to any promoter and any 3' UTR is introduced into any animal at any time (before, after, or during pregnancy) by any method/route so as to increase growth of the offspring." The Examiner selected Khan et al. (2002, Endocrinology) and Kahn et al. (2003, Amer. J. Physiol) to illustrate that even post-filing studies have demonstrated examples that gene therapy, a general method, is unpredictable. In the First Office Action, the Examiner points out that while Khan et al.'s study demonstrated that mother rats injected with a nucleic acid construct comprising a nucleic acid sequence encoding GHRH did result in transfer of GHRH protein to the fetus and offspring, the Examiner also points out that there is no way of controlling the expression of the gene and therefore, delivery of the protein to the fetus could not be controlled and as seen, this would lead to muscle hypertrophy in the offspring (First Office Action, page 3, 3rd parag. to page 4, 1st parag.). This inability to control expression of the gene and delivery of protein to the fetus is one uncertain factor of gene therapy. The Applicants counter this argument by stating that hypertrophy is a temporary issue ("the rats had increased body weights to 10 weeks of age, but by 24 weeks of age the difference was no longer significant"(Applicant's Response, page 18, 4th parag., lines 2-3))." In addition to this, the Applicants stress that this faster maturation of the rat offspring is within PHYSIOLOGICAL (Applicant emphasis) stimulation of the GHRH axis and not to an unpredictable "in utero gene therapy (Applicant's Response, page 18, 4th parag., lines 5-6)." The Applicants also point out that "there is no description of muscle hypertrophy in the pigs (Applicant's Response, page 19, 1st parag., lines 2-3)." It should be pointed out that despite the fact that the

Applicants point out that in the end run that there does not appear to be any overt mal effects of the GHRH treatment, the effect of GHRH is not the focus of the argument. Rather, the focus is that the effect of GHRH on animals is unpredictable. In fact, as taught by the applicants, the pigs and rats have different phenotypic responses to GHRH is one of the issues of unpredictability of gene therapy. It thus follows that the Applicants correctly point out to disagree with the fact that there is no way of knowing whether humans would demonstrate hypertrophy when exposed to GHRH in utero (Applicant's Response, page 19, 2nd parag. and 3rd parag. lines 1-2). In light of the fact that gene expression cannot be controlled and subsequent delivery of the protein to the fetus cannot be controlled and that pigs, rats, and possibly humans have different phenotypic responses to GHRH is the very reason why a skilled artisan is not enabled for "any nucleic acid linked to any promoter and any 3' UTR is introduced into any animal at any time (before, after, or during pregnancy) by any method/route so as to increase growth of the offspring." The Applicants have not provided any substantial evidence as to why they are enabled for the broad scope of "any nucleic acid linked to any promoter and any 3' UTR is introduced into any animal at any time (before, after, or during pregnancy) by any method/route so as to increase growth of the offspring."

Regarding the Applicant's argument to plasmid DNA not crossing to the fetus in a method for "in utero fetal gene therapy, (Applicant's Response, page 19, 3rd parag.)" the Applicant's argument was based on the Applicant's definition of "in utero gene therapy." Applicant's own argument supports the stand taken in the previous Office Action that gene therapy was not enabled for "any nucleic acid linked to any promoter and any 3'

UTR is introduced into any animal at any time (before, after, or during pregnancy) by any method/route so as to increase growth of the offspring." The Applicant points out that in a study by Khan et al. (2003, Amer. J. Physiol.) that "plasmid does not circulate from the injection point and all samples from sow's milk, colostrums, aminotic fluid, placenta, and from offspring liver were negative for the presence of plasmid. Thus, the study indicates that no plasmid crosses to the fetus, so the therapy is not and cannot be an in utero fetal gene therapy (Applicant's Response, page 19, 3rd parag. lines 4-8)." In this argument, the Applicant is further supporting the stand taken in the previous Office Action, "any nucleic acid linked to any promoter and any 3' UTR is introduced into any animal at any time (before, after, or during pregnancy) by any method/route so as to increase growth of the offspring."

With regards to the Applicant's argument regarding Stribley et al. (2002, Fertility and Sterility), while the Applicant does point out the aspects of the invention that did work (Applicant's Amendment, page 19, 4th parag. to page 20, 1st parag.) the Applicant does not provide an argument, nor any evidence as to why demonstrating the one example, the instant invention, provides enablement for the broad scope of the claims as written: "any nucleic acid linked to any promoter and any 3' UTR is introduced into any animal at any time (before, after, or during pregnancy) by any method/route so as to increase growth of the offspring." In addition to this, the Applicant provides an argument that the claimed invention does not require viral vectors, such as adenoviruses, retroviruses, or adeno-associated viruses which are discussed by Stribley. This statement by the Applicant is a limitation of the claims for viral vector. However, the

claims as they presently stand, encompass these viral vectors (see claim 1, line 2, "an effective amount of a vector." Furthermore, while Stribley does not entirely rule out feasability, it should be pointed out that at the same time Stribley does not teach how use a viral vector such that it functions in a predictable manner. Similarly, with regards to Anderson (1998, Nature), while the Applicant points to Anderson's statement that "although viral systems are potentially very efficient, two factors suggest that non-viral (i.e. plasmid DNA) gene delivery systems will be the preferred choice in the future: safety and ease of manufacturing." However, neither Anderson nor the Applicant teach a method enabling all DNA vectors. For this reason, the Applicant is not enabled for the broad scope of all vectors.

With regards to Romano et al. (2000, Stem Cells) (Applicant's Amendment, page 21, 2nd parag.), the Examiner provided the reference to emphasize the point that the entire scope of the claimed invention is not enabled and that gene therapy as a general and routinely practiced method was not enabled. Romano et al. taught the "unpredictability with the issues of vectors, promoter, route of administration." Romano et al.'s example was that gene therapy, using viral vectors, was used to target infectious diseases, in particular HIV/AIDS. Romano teach the use of "in utero gene therapy" as "another line of intervention" that was recently proposed. While the Applicant argues that the scope of Romano et al. ("in utero gene therapy") is not the same scope as that of the Applicant, it should be pointed out that the claims as they stand encompass "in utero gene therapy."

The Applicants argue the distinctions between the instant Invention and the teachings in the art. In fact, the Applicants do provide an argument that, in fact, the claimed Invention really is only a small scope of the full breadth of the claims. However, the claims as they stand remain broad. For this reason, the Applicant's amendment to the claim 1, by inserting the phrase, "either diploid or muscle" cells does not overcome the rejection. Adding "either diploid or muscle" to the claim does not obviate the rejection. The art teaches that there is "unpredictability with the issues of vectors, promoter, route of administration (see Romano, above)." "Diploid" cells include brain and skin cells. In view of what has been taught in the art, the administration and expression of vectors in brain cells and skin cells is not predictable. Further, nothing in the specification or the art teaches that injection into diploid cells such as skin cells and brain cells would be successful vehicles for producing GHRH protein, nor does the art or the specification teach that GHRH protein produced by diploid cells such as skin or brain cells would be an effective way of introducing GHRH to a fetus or offspring. For this reason, the rejection is maintained.

35 U.S.C. 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The 35. U.S.C. 112, second paragraph rejection of claims 11 and 86 has been *withdrawn*. The Applicant has amended the claims.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

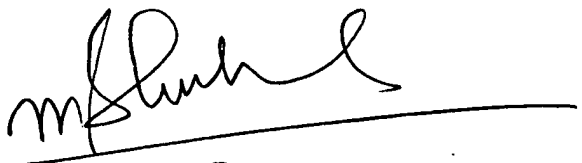
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

JH



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